

APPLICANT FACSIMILE OF FORM PTO-1449  
REV 7-80

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

ATTY DOCKET NO.

BBI-013C3CN2

SERIAL NO.

09/281,674

APPLICANT

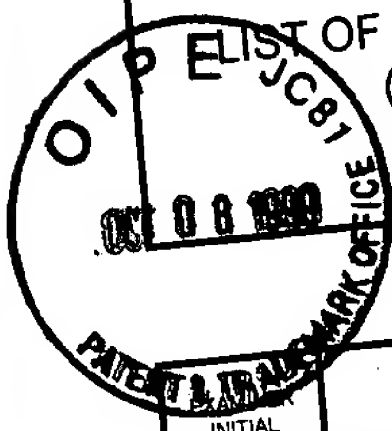
Bujard, H., Gossen, M., Salfeld, J. and Voss, J

FILING DATE

March 20, 1999

GROUP

4643-1632



LIST OF PUBLICATIONS CITED BY APPLICANT  
(Use several sheets if necessary)

U.S. PATENT DOCUMENTS

INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
m	AA 5,221,778	6/93	Byrne et al.	800	2	
m	AB 4,833,080	05/89	Brent et al.	435	172.3	

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
m	AC WO 94/04672	03/94	PCT				
	AD WO 92/20808	11/92	PCT				
	AE WO 91/19784	12/91	PCT				
	AF WO 93/04169	03/93	PCT				
	AG WO 91/19796	12/91	PCT				
	AH WO 92/11874	07/92	PCT				
	AI EP 0 332 416	09/89	EPO				
	AJ WO 93/23431	11/93	PCT				
	AK WO 94/18317	08/94	PCT				
	AL 0 455 687 B1	11/91	EPO				
	AM 0 455 424 A3	11/91	EPO				
m	AN 0 494 724 A2	07/92	EPO				

OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

m	AO	Fieck, A., et al., (1992) "Modification of the E. Coli Lac Repressor for Expression in Eukaryotic Cells: Effect of Nuclear Signal Sequence on Protein Activity and Nuclear Documentation", <i>Nucleic Acid Research</i> , Vol. 20, pp. 1785-1791;
	AP	Seipel, K., et al., (1992) "Different activation domains stimulate transcription from remote ('enhancer') and proximal ('promoter') positions", <i>The EMBO Journal</i> , Vol. 11, No. 13, pp. 4961-4968;
m	AQ	Epstein-Baak, R., et al., (1992) "Inducible Transformation of Cells from Transgenic Mice Expressing SV40 under Lac Operon Control", <i>Cell Growth &amp; Differentiation</i> , Vol. 3, pp. 127-134;
Examiner		Date Considered 5/21/00
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AR

Gossen, M., and Bujard, H., (1992) "Tight control of gene expression in mammalian cells by tetracycline-responsive promoters", *Proceedings of the National Academy of Science*, Vol. 89, pp. 5547-5551;

AS

Bradley, A., (1991) "Modifying the mammalian genome by gene targeting", *Current Opinion in Biotechnology*, Vol. 2, pp. 832-829;

AT

Wyborski, D.L., and Short, J.M., (1991) "Analysis of Inducers of the *E. Coli* Lac Repressor System in Mammalian Cells and Whole Animals", *Nucleic Acid Research*, Vol. 19, pp. 4647-4653;

AU

Degenkolb, J., et al., (1991) "Structural Requirements of Tetracycline-Tet Repressor Interaction: Determination of Equilibrium Binding Constants for Tetracycline Analogs with the Tet Repressor", *Antimicrobial Agents and Chemotherapy*, Vol. 35, No. 8, pp. 1591-1595;

AV

Baim, S.B., et al., (1991) "A chimeric mammalian transactivator based on the *lac* repressor that is regulated by temperature and isopropyl  $\beta$ -D-thiogalactopyranoside", *Proceedings of the National Academy of Science*, Vol. 88, pp. 5072-5076;

AW

Gatz, C., et al., (1991) "Regulation of a modified CaMV 35S promoter by the Tn 10-encoder Tet receptor in transgenic tobacco", *Mol. Gen. Genet.*, Vol. 227, No. 2, pp. 229-237;

AX

Labow, M.A., et al., (1990) "Conversion of the *lac* Repressor into an Allosterically Regulated Transcriptional Activator for Mammalian Cells", *Molecular and Cellular Biology*, Vol. 10, No. 7, pp. 3343-3356;

AY

Deuschle, U., et al., (1989) "Regulated expression of foreign genes in mammalian cells under the control of coliphage T3 RNA polymerase and *lac* repressor", *Proceedings of the National Academy of Science*, Vol. 86, pp. 5400-5404;

AZ

Capecchi, M.R., (1989) "Altering the Genome by Homologous Recombination", *Science*, Vol. 244, pp. 1288-1292;

BA

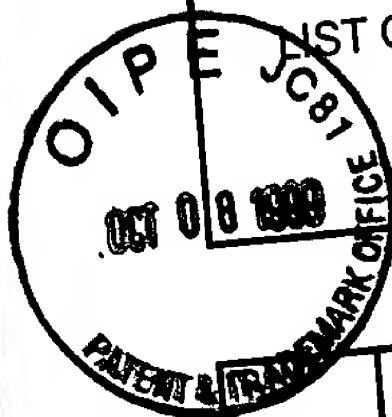
Mermod, N., et al., (1989) "The Proline-Rich Transcriptional Activator of CTF/NF-1 Is Distinct from the Replication and DNA Binding Domain", *Cell*, Vol. 58, 741-753;

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BR	Mansour, S.L., et al., (1988) "Disruption of the proto-oncogene <i>int-2</i> in mouse embryo-derived stem cells: a general strategy for targeting mutations to non-selectable genes", <i>Nature</i> , Vol. 336, pp. 348-352;
BC	Gatz, C., and Quail, P.H., (1988) "Tn10-encoded <i>tet</i> repressor can regulate an operator-containing plant promoter", <i>Proceedings of the National Academy of Science</i> , Vol. 85, pp. 1394-1397;
BD	Figge, J., et al., (1988) "Stringent Regulation of Stably Integrated Chloramphenicol Acetyl Transferase Genes by <i>E. coli lac</i> Repressor in Monkey Cells", <i>Cell</i> , Vol. 52, 713-722;
BE	Triezenberg, S.J., et al., (1988) "Functional dissection of VP16, the <i>trans</i> -activator of herpes simplex virus immediate early gene expression", <i>Genes &amp; Development</i> , Vol. 2, pp. 718-729;
BF	Courey, A.J., and Tjian, R., (1988) "Analysis of Sp1 <i>In Vivo</i> Reveals Multiple Transcriptional Domains, Including a Novel Glutamine-Rich Activation Motif", <i>Cell</i> , Vol. 55, pp. 887-898;
BG	Tovar, K., et al., (1988) "Identification and nucleotide sequence of the class E <i>tet</i> regulatory elements and operator and inducer binding of the encoded purified Tet repressor", <i>Mol. Gen. Genet.</i> , Vol. 215, pp. 76-80;
BH	Brown, M., et al., (1987) " <i>lac</i> Repressor Can Regulate Expression from a Hybrid SV40 Early Promoter Containing a <i>lac</i> Operator in Animal Cells", <i>Cell</i> , Vol. 49, pp. 603-612;
BI	Hu, M.C-T and Davidson, N., (1987) "The Inducible <i>lac</i> Operator-Repressor System Is Functional in Mammalian Cells", <i>Cell</i> , Vol. 46, pp. 555-566;
BJ	Smithies, O., et al., (1985) "Insertion of DNA sequences into the human chromosomal $\beta$ -globin locus by homologous recombination", <i>Nature</i> , Vol. 317, pp. 230-234;
BK	Boshart, M., et al., (1985) "A Very Strong Enhancer Is Located Upstream of an Immediate Early Gene of Human Cytomegalovirus", <i>Cell</i> , Vol. 41, No. 2, pp. 521-530;
BL	Brent, R. and M. Ptashne (1984) "A Bacterial Repressor Protein or a Yeast Transcriptional Terminator Can Block Upstream Activation of A Yeast Gene" <i>Nature</i> 312:612-615;

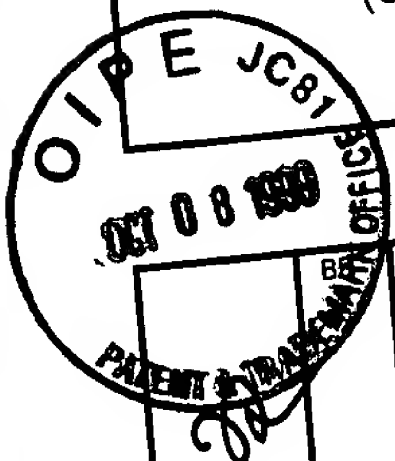
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BM

Brent R. and M. Ptashne (1985) "A Eukaryotic Transcriptional Activator Bearing the DNA Specificity of a Prokaryotic Repressor" Cell 43:729-736;

BN

Postle, K., et al., (1984) "Nucleotide sequence of the repressor gene of the TN10 tetracycline resistance determinant", *Nucleic Acid Research*, Vol. 12, No. 12, pp. 4849-4863;

BO

Unger, B., et al., (1984) "Nucleotide sequence of the gene, protein purification and characterization of the pSC101-encoded tetracycline resistance-gene-repressor", *Gene*, Vol. 31, pp. 103-108;

BP

Unger, B., et al., (1984) "Nucleotide sequence of the repressor gene of the RA1 tetracycline resistance determinant: structural and functional comparison with three related Tet repressor genes", *Nucleic Acid Research*, Vol. 12, No. 20, pp. 7693-7703;

BQ

Waters, S.H., et al., (1983) "The tetracycline resistance determinants of RP1 and Tn1721: nucleotide sequence analysis", *Nucleic Acid Research*, Vol. 11, No. 17, pp. 6089-6105;

BR

Hillen, W., and Schollmeier, K., (1983) "Nucleotide sequence of the Tn10 encoded tetracycline resistance gene", *Nucleic Acid Research*, Vol. 11, No. 2, pp. 525-539;

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EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

## FOREIGN PATENT DOCUMENTS

DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES NO

## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

<i>gn</i>	BS	Bergman, M. et al., "Overexpressed Csk Tyrosine Kinase is Localized in Focal Adhesions, Causes Reorganization of $\alpha v \beta 5$ Integrin, and Interferes with He La Cell Spreading", <i>Molecular and Cellular Biology</i> , Vol. 15 (2), pp. 711-722 (1995);
	BT	Buckbinder, L. et al., "Gene Regulation by Temperature-Sensitive p53 Mutants: Identification of p53 Response Genes", <i>PNAS</i> , Vol. 91, pp. 10640-10644 (1994);
	BU	Damke, H. et al., "Induction of Mutant Dynamin Specifically Blocks Endocytic Coated Vesicle Formation", <i>The Journal of Cell Biology</i> , Vol. 127 (4), pp. 915-934 (1994);
	BV	Damke, H. et al., "Tightly Regulated and Inducible Expression of Dominant Interfering Dynamin Mutant in Stably Transformed HeLa Cells", <i>Methods in Enzymology</i> , Vol. 257, pp. 209-220 (1995);
	BW	Dhawan, J. et al., "Tetracycline-Regulated Gene Expression Following Direct Gene Transfer into Mouse Skeletal Muscle", <i>Somatic Cell and Molecular Genetics</i> , Vol. 21 (4), pp. 233-240 (1995);
	BX	Efrat, S. et al., "Conditional Transformation of a Pancreatic $\beta$ -cell line Derived from Transgenic Mice Expressing a Tetracycline-regulated Oncogene", <i>PNAS</i> , Vol. 92, pp. 3576-3580 (1995);
	BY	Englert, C. et al., "WT1 Suppresses Synthesis of the Epidermal Growth Factor Receptor and Induces Apoptosis", <i>EMBO Journal</i> , Vol. 14 (19), pp. 4662-4675 (1995);
	BZ	Fishman, G. et al., "Tetracycline-regulated Cardiac Gene Expression in Vivo", <i>Journal of Clinical Investigation</i> , Vol. 93, pp. 1864-1868 (1994);
	CA	Fruh, K. et al., "Displacement of Housekeeping Proteasome Subunits by MHC-encoded LMPs: a Newly Discovered Mechanism for Modulating the Multicatalytic Proteinase Complex", <i>EMBO Journal</i> , Vol. 13 (14), pp. 3236-3244 (1994);
	CB	Fruh, K. et al., "A Viral Inhibitor of Peptide Transporters for Antigen Presentation", <i>Nature</i> , Vol. 375, pp. 415-418 (1995);
	CC	Haase, S. et al., "Transcription Inhibits the Replication of Autonomously Replicating Plasmids in Human Cells", <i>Molecular and Cellular Biology</i> , Vol. 14 (4), pp. 2516-2524 (1994);
	CD	Hennighausen, L. et al., "Conditional Gene Expression in Secretory Tissues and Skin of Transgenic Mice Using the MMTV-LTR and the Tetracycline Responsive System", <i>Journal of Cellular Biochemistry</i> , Vol. 59, pp. 463-472 (1995);
<i>gn</i>	CE	Maheswaran, S. et al., "The WT1 Gene Product Stabilizes p53 and Inhibits p53-mediated Apoptosis", <i>Genes &amp; Development</i> , Vol. 9, pp. 2143-2156 (1995);
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<input checked="" type="checkbox"/>	CM	5,464,758	11/95	Gossen et al.	435	69.1	
<input checked="" type="checkbox"/>	CN	5,545,808	8/96	Hew et al.	800	2	
<input checked="" type="checkbox"/>	CO	5,595,895	1/97	Miki et al.	435	172.3	

## FOREIGN PATENT DOCUMENTS

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							YES	NO
<input checked="" type="checkbox"/>	CP	WO 96/01313	01/96	PCT				
<input checked="" type="checkbox"/>	CQ	WO 94/29442	12/94	PCT				
<input checked="" type="checkbox"/>	CR	WO 91/13979	9/91	PCT				

## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

<input checked="" type="checkbox"/>	CS	Ackland-Berglund, C.E. and Leib, D.A. (1995) BioTechniques 19:216-217;
<input checked="" type="checkbox"/>	CT	Ackland-Berglund, C.E. and Leib, D.A. (1995) "Efficacy of Tetracycline-Controlled Gene Expression Is Influenced by Cell Type" <i>BioTechniques</i> 18(2):196-200;
<input checked="" type="checkbox"/>	CU	Agarwal, M.L. et al., "p53 Controls Both the G <sub>2</sub> /M and the G <sub>1</sub> Cell Cycle Checkpoints and Mediates Reversible Growth Arrest in Human fibroblasts," <i>Proceedings of the National Academy of Science, Sci. USA</i> , 92: pp. 8493-8497 (1995);
<input checked="" type="checkbox"/>	CV	Altschmied, L. et al., (1988) "A threonine to alanine exchange at position 40 of Tet repressor alters the recognition of the sixth base pair of <i>tet</i> operator from GC to AT", <i>The EMBO Journal</i> , 7(12):4011-4017;
<input checked="" type="checkbox"/>	CW	Baniahmad, A. et al. (1992) "A Transferable Silencing Domain Is Present In the Thyroid Hormone Receptor, In the v-erbA Oncogene Product and In the Retinoic Acid Receptor" <i>The EMBO Journal</i> 11(3):1015-1023;
<input checked="" type="checkbox"/>	CX	Baumeister, R. et al.(1992)"Tet Repressor Tet Operator Interactions Derived From Mutants With New Recognition Specificities", <i>Structural Tools For The Analysis Of Protein-Nucleic Acid Complexes Advances In Life Sciences</i> , Birkhauser, Basel ;Boston, pp. 175-183;
<input checked="" type="checkbox"/>	CY	Baumeister, R. et al.(1992)"Contacts Between Tet Repressor And Tet Operator Revealed By New Recognition Specificities Of Single Amino Acids Replacement Mutants", <i>Journal Of Molecular Biology</i> , Vol. 226, pp. 1257-1270;
<input checked="" type="checkbox"/>	CZ	Baumeister, R. et al.(1992)"Functional Roles Of Amino Acid Residues Involved In Forming THE.Alpha.-helix-turn-.alpha.-helix operator DNA Binding Motif Of Tet repressor From Tn10", <i>Proteins: Structure, Function, and Genetics</i> , Vol. 14(2), pp. 168-177;
<input checked="" type="checkbox"/>	DA	Bradley, A., (1992)"Modifying The Mouse: Design And Desire", <i>Biotechnology</i> , Vol. 10, pp. 534-539;

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		Cayrol, C. et al. "Identification of Cellular Target Genes of the Epstein-Barr Virus Transactivator Zta: Activation of Transforming Growth Factor $\beta$ h3 (TGF- $\beta$ h3) and TGF- $\beta$ 1", <i>Journal of Virology</i> , 69, No. 7, pp. 4206-4212, (1995);
	DC	Chen, Y.Q. et al. "Tumor Suppression by p21 <sup>WAF1</sup> ", <i>Cancer Research</i> , 55, pp. 4536-4539, (1995);
	DD	Coghlan, A. "Gene dream fades away" <i>New Scientist</i> 148, pp. 14-15, (1995);
	DE	Cowell, "Repression versus activation in the control of gene transcription," <i>Trends in Biochemical Sciences</i> , 19:1, 38-42 (1994);
	DF	Crystal, R.G. "Transfer of Genes to Humans: Early Lessons and Obstacles to Success", <i>Science</i> 270, pp. 404-410 (1995);
	DG	Daddona et al., "Human Adenosine Deaminase." <i>J. Biol. Chem.</i> 259: 12101-12106(1984);
	DH	Deuschle et al., "Tetracycline-reversible silencing of eukaryotic promoters," <i>Mol. Cell. Biol.</i> , 15:4, 1907-1914 (1995);
	DI	Ebert, K.M. et al. (1988) "A Moloney MLV-Rat Somatotropin Fusion Gene Produces Biologically Active Somatotropin in a Transgenic Pig." <i>Molecular Endocrinology</i> 2(3): 277-283;
	DJ	Fields, S. et al (1989) "A novel genetic system to detect protein-protein interactions" <i>Nature</i> 340: 245-246;
	DK	Figge, J., et al., (1988) "Stringent Regulation of Stably Integrated Chloramphenicol Acetyl Transferase Genes by <i>E. coli lac</i> Repressor in Monkey Cells", <i>Cell</i> 52:713-722;
	DL	Frankel, F.D. et al (1988) "Tat Protein from Human Immunodeficiency Virus Forms a Metal-Linked Dimer" <i>Science</i> 240: 70-73;
	DM	Furth P. (1994) "Temporal Control of Gene Expression in Transgenic Mice By A Tetracycline-Responsive Promoter" <i>Proc. Natl. Acad. Sci. USA</i> 91:9302-9306;
	DN	Gatz et al. "Stringent repression and homogeneous de-repression by tetracycline of a modified CaMV 35S promoter in intact transgenic tobacco plants," <i>The Plant Journal</i> , 2:3, 397-404 (1992);
	DO	Gatz, C. et al. "Regulation of a modified CaMV 35S Promoter by the Tn 10-encoder Tet repressor in Transgenic Tobacco" <i>Mol. Gen. Genet.</i> 227(2):229-237 (1991);
	DP	Gjetting, T. et al. "Regulated Expression of the Retinoblastoma Susceptibility Gene in Mammary Carcinoma Cells Restores Cyclin D1 Expression and G <sub>1</sub> -Phase Control", <i>Biol. Chem. Hoppe-Seyler</i> , 376, pp. 441-446 (1995);
	DQ	Gossen M. and B. Hermann (1993) "Anhydrotetracycline, A Novel Effector of Tetracycline Controlled Gene Expression Systems In Eukaryotic Cells" <i>Nucleic Acids Research</i> 21(18):4411-4412;
	DR	Gossen, M., et al., (1993) "Control of gene activity in higher eukaryotic cells by prokaryotic regulatory elements", <i>TIBS</i> 18(12):471-475;

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		Gossen et al., "Exploiting prokaryotic elements for the control of gene activity in higher eukaryotics," Keystone Symposium on Gene Therapy and Molecular Medicine, Steamboat Springs, Colorado, <i>Journal of Cellular Biochemistry</i> , Supplement 0 (21A), Abstract no. C6-220, 355 (1995);
	DT	Gossen et al. (1994) "Inducible Gene Expression Systems For Higher Eukaryotic Cells" <i>Current Opinion in Biotechnology</i> 5:516-520;
	DU	Gossen et al., "Transcriptional activation by tetracyclines in mammalian cells," <i>Science</i> , 268:5218, 1766-1769 (1995);
	DV	Gunzburg, W.H. and Salmons, B. "Virus vector design in gene therapy", <i>Molecular Medicine Today</i> 1, pp. 410-417, (1995);
	DW	Hammer, R.E. et al. (1986) "Genetic Engineering of Mammalian Embryos." <i>J. Anim. Sci.</i> 63: 269-278;
	DX	Hecht, B., et al., (1993) "Noninducible Tet Repressor Mutations Map from the Operator Motif to the C Terminus", <i>Journal of Bacteriology</i> 175(4);
	DY	Herschbach B. and A. Johnson (1993) "Transcriptional Repression In Eukaryotes" <i>Annu. Rev. Cell Biol.</i> 9:479-509;
	DZ	Hinrichs, W., et al., (1994) "Structure of the Tet Repressor-Tetracycline Complex and Regulation of Antibiotic Resistance", <i>Science</i> 264:418-420;
	EA	Howe, J.R. et al., (1995) "The Responsiveness of a Tetracycline-Sensitive Expression System Differs in Different Cell Lines", <i>The Journal of Biological Chemistry</i> , 270, No. 23, pp. 14168-14174;
	EB	Houdebine, L.-M. (1994) "Production of Pharmaceutical Proteins From Transgenic Animals", <i>Journal Of Biotechnology</i> Vol. 34, pp. 269-287;
	EC	Kao, C.C., et al. (1990) "Cloning of a Transcriptionally Active Human TATA Binding Factor" <i>Science</i> 248: 1646-1650;
	ED	Kappel, C.A., et al., (1992) "Regulating Gene Expression In Transgenic Animals", <i>Current Opinion In Biotechnology</i> , Vol. 3, pp. 548-553;
	EF	Krimpenfort, P. et al. "Generation of Transgenic Dairy Cattle Using 'in vitro' Embryo Production." <i>BIO/Technology</i> 9, pp. 844-847 (1991);
	EG	Landschulz, W.H. et al. (1989) "The DNA Binding Domain of the Rat Liver Nuclear Protein C/EBP is Bipartite" <i>Science</i> 243: 1681-1688;
	EH	Liang et al., (1995) "Enhanced and switchable expression systems for gene-transfer," Keystone Symposium on Gene Therapy and Molecular Medicine, Steamboat Springs, Colorado, <i>Journal of Cellular Biochemistry</i> , Supplement 0 (21A), Abstract no. C6-220, 379;
	EI	Licht, J. et al. (1990) "Drosophila Krüppel Protein is a Transcriptional Repressor" <i>Nature</i> 346:76-79;
	EJ	Marshall, E. "Gene Therapy's Growing Pains" <i>Science</i> 269, pp. 1050-1055 (1995);
	EK	Mastrelangelo et al "Gene Therapy for Human Cancer: An Essay for Clinicians" <i>Seminars in Oncology</i> 23 (1), pp. 4-21 (1996);

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## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

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Initial if reference considered, whether or not citation is in conformance with MPEP 609;  
Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

**LIST OF PUBLICATIONS CITED BY APPLICANT**  
(Use several sheets if necessary)

**BBI-013C3CN2**

**09/281,674**

**APPLICANT**

**Bujard, H., Gossen, M., Salfeld, J. and Voss, J.**

FILING DATE

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**03/30/1999**

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**\*EXAMINER:**

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